Conclusions: Our AEI results suggest that cis-acting regulatory polymorphisms acting on GNL3 and SPCS1 contribute to the OA association signal at chromosome 3p21. The SNP used to study AEI for GNL3 was rs11177 whilst the one used for SPCS1 was rs6617. These two SNPs are in high LD with each other ($r^2 = 0.93$), such that the minor alleles for both SNPs are inherited together in a haplotype that correlates tightly with the association signal. As both genes show reduced expression of the OA-associated allele, it seems possible that they are co-ordinately regulated. Functionally, although the association signal correlates with only a small decrease in expression of each gene, an individual carrying the associated allele will carry the shared haplotype and shall therefore be subjected to the combined effect of a lower expression of both genes. We hypothesise that this combined effect contributes to the increased risk of developing OA that maps to this region of the genome. SPCS1 codes for signal peptidase complex subunit 1 homolog, a subunit of a complex that acts to cleave signal sequences from secretory and membrane proteins in the lumen of the endoplasmic reticulum. GNL3 codes for guanine nucleotide binding protein-like 3, also known as nucleostemin. This protein is concentrated in stem cell nucleoli, and is known to modulate p53 function, thereby performing a role in cell cycle regulation and cell proliferation and self-renewal. GNL3 also has a broader role in maintenance of nucleolar structure and telomerase activity. Our results now justify much more detailed investigation of these two genes, and of their encoded proteins, in the context of OA etiology.

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IS TYPE 2 DIABETES RELATED TO OSTEOARTHRITIS? A MENDELIAN RANDOMISATION STUDY THAT INVESTIGATES GLYCEMIC TRAITS AND OSTEOARTHRITIS

T.A. Hoeven, P.S. de Vries, A. Dehghan, O.H. Franco, A. Hofman, P.J. Bindels, S.M. Bierma-Zeinstra, J.B. van Meurs. *Erasmus Univ. Med. Ctr., Rotterdam, Netherlands*

Purpose: Previous studies examining the relationship between type 2 diabetes mellitus (DM) and osteoarthritis (OA) have presented conflicting results that are further hampered by methodological issues such as reverse causality, measurement error or possible confounding by lifestyle factors and baseline health status. Hence, it remains unclear whether DM and OA are associated and/or causally related. One way to address causation in epidemiology, particularly in chronic diseases, is the use of mendelian randomization. The random assortment of alleles at the time of gamete formation results in population distributions of genetic variants that are generally independent of behavioral factors that confound epidemiological associations. In other words, mendelian randomization through genetic risk factors might overcome confounding and reverse causality, which hamper the interpretation of classical epidemiological studies. We therefore investigated whether genetically defined elevated levels of glycemic traits (fasting glucose and fasting insulin) were associated with the presence of OA of the knee, hip and hand in a large population-based study.
Methods: In a population-based cohort study involving participants aged 45 years and older (the Rotterdam Study), genotypes and covariates were collected at baseline (n = 10,213; mean age 66.0 years; 41% men). We constructed weighted genetic risk scores based on single-nucleotide polymorphisms (SNPs) known to be associated with fasting insulin (n = 11 SNPs) or fasting glucose (n = 36 SNPs), independent of body mass index. SNPs that were known to be associated with both fasting insulin and fasting glucose levels were excluded. X-rays were scored using the Kellgren–Lawrence score for OA at baseline and osteoarthritis was defined as a Kellgren–Lawrence score $\geq$2. We analysed the genetic risk scores for their association with presence of OA using logistic regression analysis.
Results: Within the study population, 17% had radiographic knee OA, 8% hip OA, and 29% hand OA. The genetic risk scores for fasting glucose and fasting insulin levels were associated with fasting glucose levels and fasting insulin levels in the population ($p = 4.39 \times 10^{-30}$, and $p = 1.77 \times 10^{-5}$ respectively) and explained 0.9% and 0.4% of the total variance of the glycemic traits. No significant association was found between the fasting insulin genetic risk and OA-prevalence. However, genetically defined higher glucose levels were associated with a lower risk for knee OA. Unadjusted analyses showed similar results.

Table
Genetic risk scores for glycemic traits in relation to prevalent OA

	Knee OA OR (95% CI)*	Hip OA OR (95% CI)*	Hand OA OR (95% CI)*
Fasting Glucose	0.91 (0.85–0.97)**	0.98 (0.90–1.07)	0.97 (0.92–1.03)
Fasting Insulin	0.98 (0.92–1.05)	0.95 (0.87–1.04)	1.00 (0.95–1.07)

*Adjusted for age, sex, body mass index, hypertension, cholesterol ratio, and smoking. **$p < 0.01$
Conclusions: In this population-based cohort study persons with increased genetic risk scores for glycemic traits were not at higher risk of OA. These first analyses using genetically defined elevated levels of fasting insulin and fasting glucose point in the direction of a non-causal role for diabetes mellitus type 2 in the development of osteoarthritis. The use of genetic risk scores might be a way to disentangle complex associations prone to confounding.

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A GENOME WIDE ASSOCIATION STUDY OF PRESSURE PAIN THRESHOLD IN THE JOHNSTON COUNTY OSTEOARTHRITIS PROJECT

Y. Liu †, A. Goode ‡, W. Maixner §, S. Smith §, J.M. Jordan †. † *Thurston Arthritis Res. Ctr., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC, USA;* ‡ *Community and Family Med., Duke Univ., Durham, NC, USA;* § *Regional Ctr. for Neurosensory Disorders, Dept. of Endodontics, Sch. of Dentistry, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Purpose: Pressure pain threshold (PPT) is a biological marker of individual pain perception that has been found to be significantly associated with symptomatic knee and hip osteoarthritis (OA). Although p in is a well-known heritable phenotype, previous studies to identify genes associated with PPT have not been conducted. The purpose of these analyses was to identify single nucleotide polymorphisms (SNPs) associated with PPT among African Americans, Caucasians and Caucasian Men and Women.
Methods: These analyses consist of 1,199 participants with complete genome enrolled in the Johnston County Osteoarthritis (JoCo) Project between 2003 and 2004. PPT measurements were averaged over three trials from left and right trapezius muscles using a standard baseline dolorimeter. Since over 63% of participants had PPT measures >4 kg we created a dichotomous variable to represent participants with low PPT (<4kg), as the referent, and high PPT ($\geq$4 kg), as the index. Genome wide genotyping was conducted among all participants using the Illumina Infinium 1M-Duo array. Single marker analysis was performed using logistic regression adjusting for sex, race, age, body mass index (BMI) and Center for Epidemiologic Studies Depression (CES-D) Scale score. Genome wide association (GWAS) analysis was conducted in Caucasians and African Americans separately. Sex specific GWAS analysis was performed in Caucasians to investigate the genetic difference between men and women. GWAS statistical significance was set at 10e-8.
Results: Participants' mean age was 68.1 (SD 9.0), 63.0% female, 36.4% African American, mean body mass index (BMI) 31.2 Kg/m^2 (SD = 7.0 Kg/m^2) and a mean Center for Epidemiologic Studies Depression (CES-D) Scale score of 6.5 (SD 7.4). Sex, age, BMI and CES-D scale were all statistically significantly associated with PPT ($p < 0.01$). GWAS analysis results indicated no SNP reached a 10e-8 significance level. Six SNPs had p-values less than 10e-7. Among these six SNPs, five are located in the coding regions of three genes (PLD5, ZNF253 and ZNF93). PLD5 (Phospholipase D Family, Member 5) had been reported to be associated with multiple sclerosis. ZNF253 and ZNF93 both belong to Zinc Finger Protein family and may be involved in transcriptional regulation. All the six SNPs are also significant in sex specific analysis. In addition, rs11916152 (located in MGLL gene) was associated with PPT in men only ($p =$ 9.83e-6) and rs6967902 (located in DYNC1I1 gene) in women only ($p = 4.71e-6$). MGLL gene plays a critical role in several physiological processes including pain while the DYNC1I1 gene is related with the